REMARKS

I. *Introduction*

Claims 1-12, 14, and 16-22 are pending, with claims 1-12 and 16-18 standing withdrawn. Claims 13 and 15 have been canceled without prejudice or disclaimer. Claims 14 and 19-21 have been amended. Claim 22 is new.

Support for the amendments to claim 14 may be found in original claims 13 and 14. Support for new claim 22 may be found in original claims 13 and 15. Claims 19-21 were amended to, among other things, replace the word "analogue" with the American spelling of the word (*i.e.*, "analog"). No new matter has been introduced by way of the amendments to the claims or by way of new claim 22.

II. *Priority*

Applicants have not yet submitted an English-language translation of the priority document, but would be happy to do so if the Examiner deems it necessary. *See* 37 C.F.R. § 1.55(a)(4)(i).

III. *Objections to the Specification*

The Patent Office has objected to the abstract for the reasons set forth on page 6 of the Office Action. Applicants submit herewith a copy of the abstract on a separate sheet. Reconsideration and withdrawal of the objection are respectfully requested.

The Patent Office has also objected to the specification because it allegedly "lacks the required format for presentation as provided in 37 C.F.R. 1.77(b)." *Office Action* at page 7. Applicants respectfully submit that it brought the format of the specification into compliance with 37 C.F.R. 1.77(b) by way of the Preliminary Amendment filed Apr 10, 2006. In the Preliminary Amendment, Applicants introduced, *e.g.*, the headings "Field of the Invention," "Background of the Invention," and "Brief Summary of the Invention." Accordingly, Applicants believe they have complied with 37 C.F.R. 1.77(b). Reconsideration and withdrawal of the objection are therefore respectfully requested.

IV. *Information Disclosure Statement*

Applicants acknowledge the Patent Office's comments on page 6 of the Office Action regarding Information Disclosure Statements. Applicants will file an Information Disclosure Statement in due course.

V. *Claim Objections*

The Patent Office has objected to claims 14 and 15 for the reasons set forth on pages 8 and 9 of the Office Action. Applicants assert that the objections to claims 14 and 15 should be overcome by the amendments to claim 14 and by the cancellation of claim 15. To the extent that the objections raised to claim 15 could apply to new claim 22, Applicants note that claim 22 does not contain the offending character shown on page 9 of the Office Action. Reconsideration and withdrawal of the objections to claims 14 and 15 are respectfully requested.

VI. *The rejections under 35 U.S.C. § 112, second paragraph should be withdrawn*

The Patent Office has rejected claims 14, 15, and 19-21 for the reasons set forth on pages 9-12 of the Office Action. Applicants assert that this rejection has been overcome and/or rendered moot by way of the present amendments.

For example, amended claim 14 should overcome any alleged lack of clarity with respect to the "structural characteristics of [the] somatostatin antagonist analogs" set forth on pages 11 and 12 of the Office Action. Further, none of the presently amended claims recite the offending term "includes." Still further, the antecedent basis rejection set forth on page 11 of the Office Action, paragraph 3, has been rendered moot as claims 14 and 22 have now been recast in independent form. Finally, the typographical error in claim 14 has been corrected. Claim 14 now recites that Y^1 is "OH" instead of "OR," as the specification makes clear was intended. *See, e.g.*, published application at ¶ [0053].

VI. *The rejections under 35 U.S.C. § 112, first paragraph (written description) should be withdrawn*

Claim 13 stands rejected under 35 U.S.C. § 112, first paragraph (written description)

for the reasons set forth on pages 12-14 of the Office Action. Applicants respectfully assert that this rejection is now moot in light of the cancellation of claim 13. Reconsideration and withdrawal of this rejection are respectfully requested.

VIII. *The rejection under 35 U.S.C. § 102(b) should be withdrawn*

Claim 13 stands rejected under 35 U.S.C. § 102(b) for the reasons set forth on pages 15 and 16 of the Office Action. Applicants respectfully assert that this rejection is now moot in light of the cancellation of claim 13. Reconsideration and withdrawal of this rejection are respectfully requested.

IX. *The rejection under 35 U.S.C. § 103(a) should be withdrawn*

Claims 13-15 and 19-21 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over M. Terzolo *et al.* (*The Journal of Clinical Endocrinology & Metabolism 85*: 1310-1315 (2000)) in view of WO02/072602 to Coy *et al.*

Applicants respectfully traverse the rejection. The claimed invention is to a method of accelerating the start of growth of quiescent follicles in non-menopausal women comprising administering to a patient in need thereof a medicament comprising a somatostatin antagonist analog having the general formula (III):

$$A_1\text{-cyclo}\{\text{D-Cys-}A_2\text{-D-Trp-}A_3\text{-}A_4\text{-Cys}\}\text{-}A_5\text{-}Y_1 \qquad \text{(III)}$$

wherein A_1, A_2, A_3, A_4, A_5, and Y_1 have the meanings recited in claim 14.

In one embodiment of the claimed invention, the medicament comprises specifically recited somatostatin antagonist analogs.

Terzolo teaches administering arginine (a putative functional somatostatin antagonist) to patients with adrenal gland tumor (incidentalomas) in order to test its capacity to increase the pituitary response to growth hormone releasing hormone (GHRH). Terzolo was aiming to (i) evaluate the pituitary growth hormone (GH) responsivity to GHRH in patients with incidentally discovered adrenal adenomas, and (ii) to investigate the effect of pretreatement with arginine, a functional somatostatin antagonist, on the GH response to GHRH in the

same patients." There does not appear to be any mention in Terzolo of the aim to administer arginine alone to non-menopausal women who *do not suffer from* incidentally discovered adrenal adenomas.

According to Terzolo, which published in 2000, there was little data regarding GH secretion in patients with adrenal incidentalomas. *Terzolo* at 1311, left col. Terzolo evaluated GH secretion in a group of patients with incidentaloma that included some pre-menopausal women. *Terzolo* at 1312, left col. In his study, Terzolo found that GH response to GHRH is "blunted" in patients "bearing adrenal incidentaloma," but could be "restored" using arginine pretreatment followed by treatment with GHRH. *Id.*, Abstract. Terzolo postulates that the arginine may act as a "functional somatostatin antagonist" since somatostatin is a known GH inhibitor. *Id.* at 1314, left col. and 1310, right col.

Coy discloses somatostatin antagonists of the general formula A^1-cyclo{D-Cys-A^2-D-Trp-A^3-A^4-Cys}-A^5-Y^1 for promoting wound healing and angiogenesis or, alternatively, for treating "short stature, cachexia, wasting, type 2 diabetes, and poor circulation." *Coy* at 6-7. Coy recognizes that these somatostatin antagonists may also promote GH and insulin secretion, hence their potential usefulness in treating diseases such as type 2 diabetes.

The Patent Office's obviousness rejection rests on the following bases: first, that Terzolo uses arginine, a "functional" somatostatin antagonist, to promote the secretion of GH; and second, that promotion of GH secretion in pre-menopausal women in the early follicular phase of the menstrual cycle accelerates the start of growth of quiescent follicles in such women. But the Patent Office doesn't provide support for either basis.

First, Terzolo does not teach or otherwise contemplate any impact of arginine administration on the ovarian function, follicular development and, more specifically on the induction of quiescent ovarian follicle growth in non-menopausal women as presently claimed. Instead, Terzolo focuses on the impact of arginine administration on a much different patient population, namely, non-menopausal women who also suffer from adrenal tumors (incidentalomas). As the Examiner rightly points out on page 15 of the Office Action, in Terzolo's study, three out of 13 patients with adrenal tumor (incidentaloma) were non-menopausal women. This is an expected proportion of age and sex distribution for this

incidentaloma patient population and is unrelated to a specific population choice aiming at a specific therapeutic effect. Terzolo discloses the administration of arginine to patients with adrenal gland tumor (incidentalomas) in order to test its capacity to increase the pituitary response to GHRH and not for the purpose of accelerating the start of growth of quiescent follicles in non-menopausal women. Applicants, in fact, offer that arginine administration to non-menopausal women will not inherently result in the acceleration of the start of growth of quiescent follicles.

It would appear that the Patent Office misunderstands the reason why Terzolo administers arginine to the sub-set of non-menopausal women at the beginning of their menstrual cycle as described in the "Materials and Methods" section in the article. The likely reason why Terzolo administers arginine in this subset of patients, at the beginning of the menstrual cycle, was to avoid variations in physiological parameters, such as menstrual variations of estrogen, since it is known that circulating estrogens modulate GH secretion. Ovesen *et al.*, *Journal of Clinical Endocrinology and Metabolism 83*: 1662-1667 (1998); *see* especially page 1662; FIGS. 2 and 3 on page 1665; and Discussion section on page 1666 (submitted as APPENDIX A). Applicants assert, in other words, that Terzolo does not administer arginine to non-menopausal women in his study for the purpose of impacting ovarian function in any way. As mentioned above, a proportion of three non-menopausal women on a total of 13 patients with adrenal tumor (incidentaloma) just happens to be the age and sex distribution for this incidentaloma patient population and is unrelated to a specific population choice aiming at a specific therapeutic effect.

Second, Terzolo *does not* teach that arginine alone promotes GH secretion; rather, he discloses that arginine pre-treatment "restores" GH response to GHRH in patients with incidental adenomas compared to healthy controls. Thus, to the extent Terzolo teaches that arginine promotes GH secretion at all, it is *in combination with GHRH* in patients suffering from adrenocortical adenomas. Accordingly, Terzolo does not provide the requisite motivation to administer arginine alone to non-menopausal women with a reasonable expectation of successfully promoting GH secretion, much less successfully accelerating the start quiescent follicular growth. It would appear from the rejection set forth in the Office Action that there is some confusion with regard to the term "Growth hormone," which is a

specific name for a pituitary hormone (GH) that exhibits a specific role in body growth during infancy and puberty and "growth of quiescent follicle," which is a generic term to describe development of an ovarian follicle.

It follows that, if one of ordinary skill in the art would not have been motivated to administer arginine alone to promote GH secretion in pre-menopausal women, he or she would have even less motivation to substitute Coy's antagonists in place of arginine to achieve the same result.

The Patent Office's second basis for rejection—that increased GH secretion in pre-menopausal women during the early follicular phase of the menstrual cycle necessarily ~~leads to~~ accelerates quiescent follicular growth in such women—is completely speculative. The Patent Office has not offered any evidence connecting increased GH secretion with accelerated growth of quiescent follicles in pre-menopausal women.

In sum, it appears that the Patent Office has laid down a patchwork of references, dealing with different diseases or conditions, with hindsight knowledge of Applicants' claimed method to reject the instant claims. This is impermissible. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

CONCLUSION

In view of the above remarks, early notification of a favorable consideration is respectfully requested.

Respectfully submitted,

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